DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

Reference Numbers: 95-1528 and 95-1529

Wayne Morges, Ph.D.
North American Vaccine, Inc.
12103 Indian Creek Court
Beltsville, MD 20705

JUL 29 1998

Dear Dr. Morges:

This letter hereby issues Department of Health and Human Services Biologics License No. 1254 to North American Vaccine, Inc., Beltsville, Maryland, in accordance with the provisions of Section 351(a) of the Public Health Service Act as amended November 21, 1997 (FDAMA; Public Law 105-115), controlling the manufacture and sale of biological products. This license authorizes you to manufacture and ship for sale, barter, or exchange in interstate and foreign commerce those products for which your company has demonstrated compliance with establishment and product standards.

Under this license you are authorized to manufacture and distribute the product Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP) for the immunization of infants and children except as a fifth dose in children who have previously received four doses of DTaP. In accordance with your approved labeling, your product will bear the trade name Certiva and will be marketed in 15 dose vials.

Manufacturing of the acellular pertussis component shall occur at your facility in Beltsville, Maryland. DTaP shall be formulated at the same facility using diphtheria and tetanus toxoid concentrates for further manufacturing use produced by Statens Seruminstitut (Department of Health and Human Services Biologics License No. 1255) under a shared manufacturing arrangement. The following animal testing will be performed at potency of the diphtheria and tetanus toxoids and general safety. The histamine sensitization assay and the animal component of the acellular pertussis potency test will be performed at

The provisional dating period for this combination product shall be 18 months from the date of manufacture when stored at 2-8 degrees Celsius. The date of manufacture is defined as the date of the initiation of the earliest valid potency test, regardless of which component of the final bulk is tested first. The provisional dating period for each individual adsorbed bulk intermediate of acellular pertussis, diphtheria and tetanus toxoids shall be 5 months from the date of adsorption for each component.

We acknowledge your commitment in your correspondence dated July 16, 1998, to complete the stability studies in order to obtain the remaining real time data to support the dating periods for the adsorbed components and final combination product, 5 months and 18 months, respectively. These data should be submitted when available. In addition, we acknowledge the commitment in the same correspondence that, starting with DTaP lot number 400022, the first three consecutive DTaP lots manufactured will be placed into your stability program. If at any time any lot fails to meet the specifications in your stability protocols, you are requested to inform CBER immediately, and these failed lots could be subject to a recall.

If you wish to request extension of the dating period beyond 18 months for the final combination product or beyond 5 months for the adsorbed bulk intermediates, you may do so by submitting Supplements to your license application along with documentation supporting the real time stability of the product. Alternatively, you may submit a stability protocol for prior approval to be used in extension of dating as a Supplement to your license application.

You are requested to submit to the Center for Biologics Evaluation and Research (CBER) samples of each future lot of bulk product together with protocols showing the results of all applicable tests. No lots of product shall be distributed until notification of release is received from the Director, CBER.

We acknowledge the following commitments made in submissions to your license application dated July 14, 16 and 23, 1998:

1. In order to obtain additional safety data for the administration of a fourth dose and to obtain a sufficient safety database for a fifth consecutive dose of Certiva, you have agreed to initiate a Phase 4

study, within 6 months post-licensure, in which 5 consecutive doses of Certiva are administered to infants and children using the recommended schedule. In addition, you have agreed to submit the results from this study when they are available.

2. You have agreed to revise the Chinese Hamster Ovary (CHO) cell assay calculation method, to make the corresponding changes to the Standard Operating Procedure (SOP) using adequate validation change control procedures, and submit this change as a Supplement to your license application by November 1, 1998.

3. You will submit the final validation summary report for the chromatographic column bioburden assay to your license application by November 1, 1998.

4. You have agreed to provide optimization procedures for the pertussis toxin purity assay within the first year following approval of Certiva, and to submit the optimized method to CBER as a Supplement to your license application.

5. You will submit the results of the initial preservative effectiveness studies on adsorbed acellular pertussis toxoid bulk, DTaP bulk, and DTaP final containers to your license application by November 1, 1998,.

6. You will submit the final validation summary report for the change in the method of determining the percent adsorption of acellular pertussis toxoid as a Supplement to your license application during the fourth quarter of 1998.

7. You have agreed to complete the validation of the residual hydrogen peroxide method and to submit the validation summary report to your license application by December 15, 1998.

8. You have set a provisional specification for your residual fetuin assay to be less than or equal to 80 nanograms of fetuin in 40 micrograms of pertussis toxin. We acknowledge your commitment to analyze the next 50 lots of pertussis toxin for this parameter, starting the week of July 27, 1998, to submit all data collected and to adjust this specification accordingly.

If the specification is adjusted, a Supplement to your license application may be required.

9. You have agreed to establish a specification for your acellular pertussis potency test which is expressed in relative terms [ratio of Geometric Mean Titer (GMT) of test vaccine to GMT of reference vaccine] and that this will be submitted as a Supplement to your license application by the end of December 1998.

Changes in the manufacturing, testing, packaging or labeling of your Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, in the supplier of the diphtheria and tetanus toxoids, or in the manufacturing facilities may require the submission of a Supplement to your license application for our review and written approval prior to implementation.

It is requested that adverse experience reports for Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, be submitted in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and that distribution reports be submitted as described (21 CFR 600.81). Since your product is categorized as a vaccine, these reports should be submitted to the Vaccine Adverse Event Reporting System (VAERS) using the pre-addressed form VAERS-1.

Please submit three copies of final printed labeling at the time of use and include part II of the label transmittal form with completed implementation information. In addition, please submit three copies of the introductory advertising and promotional labeling. You may wish to submit the proposed materials in draft form with an FDA Form 2567 to CBER, Advertising and Promotional Labeling Staff, HFM-202, 1401 Rockville Pike, Rockville, MD 20852-1448. Promotional claims should be consistent with and not contrary to approved labeling. No comparative claims or claim of superiority over other similar products should be made unless data to support such claims are submitted to and approved by CBER.

It is requested that you acknowledge receipt of the enclosed Biologics License to the Director, Division of Vaccines and Related Products Applications, HFM-475.

Sincerely yours,

Steven Masiello
Acting Director
Office of Compliance
and Biologics Quality
Center for Biologics
Evaluation and Research

M. Carolyn Hardegree, M.D.
Director
Office of Vaccines
Research and Review
Center for Biologics
Evaluation and Research